REMARKS

This Reply responds to each rejection raised in the Office Action mailed December 27, 2002.

Before addressing each rejection, it is important to understand the claimed invention. Applicants have discovered that fibrin-binding domains of human fibronectin should be combined with a plasminogen-activating streptokinase component as a single polypeptide molecule, to provide an unexpected benefit: *viz.* plasminogen activation by the streptokinase component is delayed or lagged. The claimed single polypeptide hybrid components are part of a single peptide molecule that includes: a) streptokinase (or modified forms of SK or parts of SK capable of plasminogen activation); and b) fibrin binding domains 4 and 5 or domains 1 and 2 (or modified forms thereof) of human fibronectin. Significantly, the resulting single polypeptide hybrid molecule possesses the ability to bind with fibrin independently, and its plasminogen activation exhibits a delay or lag.

The claims are not anticipated by or obvious from the prior art as detailed in parts **I.** and **J.** below.

A. Title

The word "novel" has been deleted from the title and editorial changes have been made.

B. Abstract

The abstract has been amended. Applicant points out that there is no requirement that the Abstract begin with a complete sentence. In fact, two of the three sample abstracts (samples (1) and (2)) provided in the MPEP at §608.01, pages 600-64 begin with noun clauses having no verb. Many (if not most) composition-of-matter patents follow that form. See, Brown U.S. 5,151,412 cited in this prosecution.

The revised abstract references fibrinogen domains as requested.

C. Figure Legends

The legends for Figs. 4 and 24 have been amended responsive to the suggestions in the office action. The suggestions are appreciated. Clarification is requested as to the legend for Fig. 7. Fig. 7 is described as,

> Restriction enzyme map of DNA encoding the five N-terminally located FBDs of human fibronectin.

The suggestion provided for that legend does not seem to apply.

D. Priority

The specification has been amended to perfect the priority claim.

E. Claim Formalities

The suggested amendments to claims 2 and 3 have been made. The suggestions are appreciated.

F. Indefiniteness

1. "pronounced" in claim 1 line 8

This term has been deleted.

2. "suitable parts"

This phrase has been deleted.

3. "various motifs"

This phrase has been deleted.

4. "suitable"

This phrase has been deleted.

5. "fibrin binding domains"

Claim 1 specifies that the fibrin binding component as "regions of human fibronectin selected from the pair of fibrin binding domains 4 and 5, or domains 1 and 2, or modified forms thereof". Those domains are well characterized in the art, e.g., in Kornblitt et al. (1985) *EMBO J.*, vol. 4, p. 1755 and in Matsuka et al. (1994) *J. Biol. Chem.* vol. 269, p.9539, each of which is discussed below and enclosed herewith. So the claim does not simply reference fibrin-binding

domains in general, it references specific domains characterized in the art, and the claim is not vague.

6. "such as" and "etc." claim 32

The phrase has been deleted.

G. Enablement

The invention is described above. The question is whether one skilled in the art could have practiced that invention based on the information provided in the specification combined with skill in the art at the time of the invention, without undue experimentation.

1. Fibrin Binding Domains

One basis for the rejection is that,

> the specification does not reasonably provide enablement for any hybrid plasminogen activator comprising...any pair of fibrin binding-domains derived from human fibronectin." (Office action page 5, lines 14-16).

Claim 1 specifies "regions of human fibronectin selected from the pair of fibrin binding domains 4 and 5, or domains 1 and 2, or modified forms thereof", i.e., it specifies certain human fibronectin binding domain pairs and not "any pair of fibrin binding-domains". The Office Action fails to analyze this specific claim language (specified pairs of fibrin binding domains of human fibronectin). Such a narrow claim scope is clearly enabled under the standards set by the Federal Circuit Court of Appeals and by the U.S. Patent and Trademark Office as detailed below.

The Office Action would limit the claims to the "fibrin binding-domain proteins as encoded by the sequences set forth in Figs 17b, 19b, 21b and 22b." (Office action page 5, lines 12-13). In other words, the Examiner is not satisfied to limit the applicants to specified domain pairs; the examiner would limit the claims to certain sequences, thus denying coverage of compositions that have a single base addition or deletion to the sequence. Such coverage is absurdly narrow, and it does no credit to the patent system to arbitrarily impose a limitation that is not warranted by the law. What is the examiner's legal and factual rationale for this extraordinarily rigid and narrow application of 35 U.S.C. §112, ¶1?

The office action cites two legal authorities: *In re Fisher*, 166 USPQ 16, 24 (CCPA 1970); and *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). First, in each of those cases the Federal Circuit or its predecessor court upheld broader claims and admonished the PTO for failing to afford proper breadth of coverage. The examiner does not explain why that controlling legal authority dictates a different result in this case. Second, those cases, particularly *In re Wands*, provide basic guidance for the enablement determination by listing the factors to be considered, such as claim scope, the skill of the art, the extent of the examples provided in the specification, the guidance provided in the specification. The Office Action does not analyze those factors, each of which supports broad coverage. For example, both the DNA an amino acid sequences of human fibronectin have been known for over 15 years. See, Kornblitt et al. (1985) *EMBO J.*, vol. 4, p. 1755. The domains of human fibronectin have been characterized. Matsuka et al. (1994) *J. Biol. Chem.* vol. 269, p.9539. Applicants have provided detailed guidance on the construction of a number of SK-FBD fusions. The claims are limited to the human fibronectin domains used in those fusions. The art was well aware of methods for determining fibronectin binding and would have had absolutely no trouble screening variants of the specified domains for the ability to bind to fibrin. The *Wands* factors support applicant's modest claim scope, and the office action provides no analysis of the *Wands* factors at all, so on this point, the Office action is not legally supported.

Regarding factual support for the rejection, at page 6, lines 3-17, the Office Action says,

> Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired plasminogen activation and fibrin binding requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i. e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein 's structure relates to its function. However, in this case the disclosure is limited to the plasminogen activators encoded by the sequences set forth in Figs 17b, 19b, 21b, and 22b.
>
> While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to

> modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The above analysis would require sequence-limited claims in every DNA or protein application presented to the PTO, yet we know that the PTO has no such blanket policy. Rather the PTO follows the Federal Circuit analysis in *Wands*. See MPEP §2164.01(a) at page 2100-179 et seq. The analysis in *Wands* supports the claims for the reasons given above.

The above rule, automatically limiting coverage to a specific example in the specificaiton is contrary to law. The MPEP specifically approves the idea that working examples can support a generic claim.

> For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art...would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. MPEP §2164.02, pp. 2100-181-182.

Most important, the rigid rule suggested in the Office Action ignores advances in the art that are now decades old, enabling the art to synthesize variants or the claimed (known) fibrin-binding domains and screen them for fibrin binding.

2. Streptokinase

In a manner similar to the rejection regarding fibrin-binding domains, the Office Action concludes that the art is not enabled to practice the claim insofar as it encompasses hybrid plasminogen activators that include "any streptokinase".

As with human fibronectin, streptokinase has been well characterized for many years. At page 9 of the specification, Applicants reference several prior art articles demonstrating the art's knowledge of streptokinase and streptokinase genetics and specifically regarding the locus of plasminogen activation,

- Jackson, KW and Tang J., 1982, *Biochemistry* vol. 21: 6620;

- Malke H., Roe B and Ferretti JJ., 1987, *Streptococcal Genetics.*, Proc. Amer. Soc. Microbiology, Wash DC. page 143;
- Kim LC, Kirn JS, Lee SH, and Byun SM, 1996, *Biochem. Mol. Bio. Int.* vol. 40: 939;
- Lee SH, Joeng ST, Kim LC, and Byun SM, 1997, *Biochem. Mol. Bio. Int.* vol. 41: 1999;
- Fay WL and Bokka LV., 1998, *Thromb Haemostasis* vol.79: 985.

Each of the above articles is enclosed.

In addition, it is known that SK has three independent, flexible domains connected to each other through flexible loops, and the ends of the molecule also contains flexible segments that are vulnerable to rapid proteolysis. See, Wang et al. (1998) *Science* vol. 281: 1662; Conejero-Lara et al. (1996) *Protein Science* vol. 5: 2583; Conejero-Lara et al. (1998) *Protein Science*, 7: 2190; Wu et al. (1998) *Appl. Environ. Microbial* vol. 64:824. Given the substantial information available to the art and the high level of skill in the art regarding streptokinase and its plasminogen activity, and the analysis required by the courts, Applicants respectfully request reconsideration of the enablement rejection.

H. Written Description

The Office Action also rejects all claims based on the lack of written description in the application. Apart from form sentences, the sum total of the analysis supporting the written description requirement is (page 8, lines 3-7),

> The claims are directed to a genus of hybrid plasminogen activator proteins. The specification teaches the structure of only four representative species of such proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a hybrid plasminogen activator.

The office action fails to conduct the analysis required in the MPEP §2163. Specifically, MPEP §2163.II.A.3.ii (page 2100-168) explains how to analyze a claim drawn to a genus,

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.
>
> * * *

> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

The application as filed is clear that Applicants intended an invention encompassing an SK component linked to various fibrin binding components in various configurations. The plasminogen activation function of the SK component is lagged or delayed. The four examples of this delay are representative and those in the art would understand that the inventors were in possession of the claimed invention.

I. Anticipation

Claim 32 has been amended to depend on claim 1, and the anticipation rejection is overcome.

J. Obviousness

The claims are rejected as obvious from Brown et al. U.S. 5,151,412 in view of Malke U.S. 5,187,098 and further in view of Atkinson U.S. 5,772,996.

The rationale for the rejection is that Brown discloses a streptokinase-fibronectin conjugate (Example E. at col. 17). Conjugation was achieved using a carbodiimide chemical cross-linking reagent, so Brown et al. does not disclose the single peptide molecule hybrid molecule of claim 1. For that aspect of claim 1, the Office Action relies on Malke, which produces a fusion of streptokinase with fibrin-binding (kringle) domains from plasminogen. The Office Action concludes that it would have been obvious to achieve streptokinase-fibronectin conjugates as taught by Brown using recombinant DNA technology (taught by Malke) in place of chemical cross-linking.

In order to provide a prima facie case of obviousness, the PTO must establish a motivation for the proposed combination of references.

> To establish a *prima facie* case of obviousness, ... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. (MPEP §2142 at 2100-24).

It is not at all clear why one skilled in the art would modify the structure of Malke et al., which already includes kringle domains to bind fibrin, by adding further fibrin binding domains. There is simply no motivation to do that.

Even if there is a prima facie case of obviousness, Applicants point out that the invention provides an unexpected advantage: the claimed single-peptide hybrid provides a desirable delay in plasminogen activation that is not taught in any way in Brown or Malke. Specifically, Applicants reference Example 8 at pages 54-59 of the specification, and Fig. 24. The invention provides a plasminogen activation function that is significantly delayed compared to the activation function of the SK component of the hybrid. This surprising result overcomes any prima facie case of obviousness. *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995).

Atkinson is cited as a tertiary reference regarding formulations and is not relevant to this issue.

Accordingly, Applicants respectfully request withdrawal of the obviousness rejection.